Treatment of complex regional pain syndrome

Matteo Longhi

U.O. Reumatologia

IRCCS Istituto Ortopedico Galeazzi- Milano

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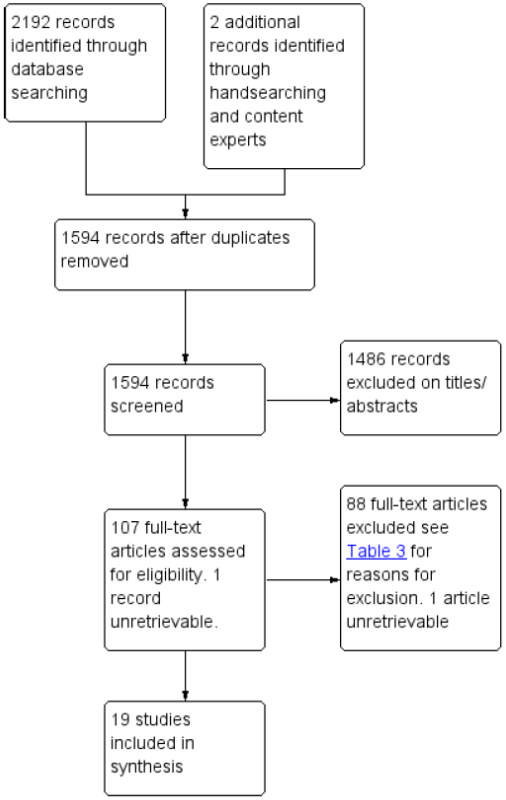
Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews (Review)

O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL

Figure 1. Study flow diagram.



High quality evidence

There is no high quality evidence for or against the effectiveness of any intervention for CRPS.

Moderate quality evidence

There is moderate quality evidence that intravenous regional blockade with guanethidine is not effective and that the procedure appears to be associated with a risk of significant adverse events.

Low quality evidence

There is low quality evidence that:

- ketamine, bisphosphonates and calcitonin may effectively reduce pain when compared with placebo at least in the short term;
- graded motor imagery (GMI) programmes may reduce pain and improve function more than conventional physiotherapy care and that these improvements are maintained at three to six months;
- mirror therapy may reduce pain and improve function more than a sham condition in post-stroke CRPS;
- topical DMSO does not improve composite CRPS scores more than N-acetylcysteine;
- local anaesthetic sympathetic blockade is not effective;
- physiotherapy or occupational therapy versus a social work passive attention control are associated with small positive effects at one year follow up that are unlikely to be clinically important.

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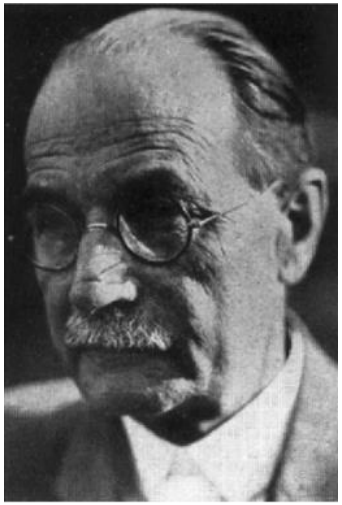
O' Connell et al. Cochrane Database Syst Rev 2013

CRPS: Historical Perspectives

- Sixteenth century Ambroise Parè described a severe and persistent pain syndrome that afflicted King Charles IX of Valois after a limb phlebotomy
- 1813 Denmark described ***sympathethic dystrophy***
- 1864 Mitchell, Moorhehouse and Keen wrote classic work describing ***causalgia*** (burning pain)
- 1864 Paget described ***skin and vasomotor changes***
- 1900 Sudeck identified ***patchy bone demineralization***
- 1923 Leriche described ***post-traumatic painful osteoporosis***
- 1947 Evans used the term ***reflex sympathethic dystrophy***
- 1947 Steinbrocker identified ***shoulder-hand syndrome***
- 1954 De Seze named the condition ***algodystrophy***
- 1973 Glick called the disease ***algo-neuro- dystrophy***
- 1990 Bonica revisited the Evans terminology ***reflex sympathetic distrophies (RDS)***
- 1994 IASP introduces the term ***Complex Regional Pain Syndrome (CRPS)***



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Casale et al. Clin Exp Rheumatol 2015
Iolascon et al. Clin Cases Min Bone Metab 2015

1994 Orlando Consensus Workshop

IASP

International Association for the Study of Pain

Reflex Symphatetic Distrophies

downsizing of the pathogenic role of the sympathetic nervous system ↓

Complex Regional Pain Syndrome

Type I, formerly known as reflex sympathetic dystrophy (RSD), Sudeck's atrophy, reflex neurovascular dystrophy (RND), or algoneurodystrophy, does not have demonstrable nerve lesions.

Type II, formerly known as causalgia, has evidence of obvious nerve damage. although the cause of the mechanisms of CRPS Type II are as unknown as the mechanisms of Type I.

Diagnostic criteria for CRPS:

IASP Diagnostic Criteria

CRPS I

1. The presence of an initiating noxious event, (or a cause of immobilization – not required for diagnosis)
2. Spontaneous occurence of pain in the absence of an external stimulus, allodynia or hyperalgesia that is not limited to the territory of a single perhipheral nerve and is disproportionate to the inciting event
3. Evidence at some time of oedema, skin blood flow abnormality or abnormal sudomotor (sweating) activity in the region of pain
4. The diagnosis in excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS II is a syndrome that develops ***after nerve iniury***

Budapest Criteria

1. Continuing pain , which in disposportionate to any inciting event
2. Must report at least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria)of the following categories: a) **Sensory**: hyperesthesia or allodynia; b) **Vasomotor**: temperatur asymmetry, skin colour changes or skin colour asymmetry; c)**Sudomotor or oedema**: oedema, sweating changes or sweating asymmetry; d) **Motor or trophic**: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia) or trophic changes (hair, nails or skin)
3. Must display at least one sign at time of of diagnosis in two or more of the following categories: **Sensory**: hyperalgesia (to pinprick) or allodynia (to light touch deep somatic pressure, or joint movement); b) **Vasomotor**: temperatur asymmetry, skin colour changes or asymmetry; c) **Sudomotor or oedema**: oedema, sweating changes or sweating asymmetry; d) **Motor or trophic**: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia) or trophic changes (hair, nails or skin)
4. No other diagnosis better explains the signs and symptoms

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modified from: Stanton-Hicks et al. Pain 1995
Harden and Bruehl. Clin J Pain 2006
Gatti et al. Osteoporos Int 2016

Etiopathogenetic conditions in CRPS-I

Peripheral tissue damages	- Bone fractures - Sprains - Soft tissue traumas - Arthitis - Immobilisation - Deep vein thrombosis
Deep visceral lesions	- Myocardial infarction - CNS lesions (traumatic, cerebrovascular) - Abdominal pathologies - Pacemaker implantation
Drugs	- Anticonvulsivants - Isoniazid - Corticosteroids

Epidemiology of CRPS-I

Limited data available.

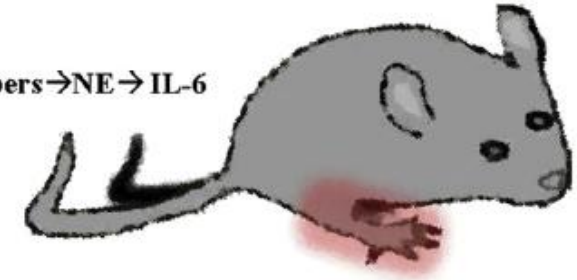
In population-based studies:
5.5 cases per 100.000 person-years in USA; 26.2 cases per 100.000 person-years in The Netherlands
In a prospective multicenter study in 596 pts with a previous fracture of feet or arms:
incidence 7% according to the Budapest criteria;
incidence 48.5% according to the IASP criteria

Female/male= 2-4/1
Peak incidence around the 4° and 6° decade
Affected sites: arm 60%, leg 40%
Triggering event: fracture ~ 45%, sprain ~ 18%, elective surgery ~ 12%

Sandroni et al. Pain 2003
de Mos et al. Pain 2007
Beerthuizen et al. Pain 2012
Marinus et al. Lancet Neurol 2011

Possible pathogenic mechanisms involved in CRPS in animal models and humans

- ○ SNS
- ➢ Neurogenic inflammation
- • Autoimmunity
- ▪ CNS



- ○ SNS fibers→NE→ IL-6

- ➢ Plasma extravasation & vasodilation
- ➢ SP & CGRP release→ keratinocyte activation → ↑ cytokines & NGF, recruitment of mast cells

- • Efficacy of anti CD-20 treatment
- • IgM deposition & complement activation in skin and nerve

- ▪ ↑ spinal inflammatory mediators
- ▪ ≠ in amygdala, perirhinal cortex, & hippocampus

- ○ Autonomic signs
- ○ Efficacy of sympatholysis in some patients

- ➢ Plasma extravasation & vasodilation
- ➢ SP & CGRP release
- ➢ ↑ cytokines & mast cells
- ➢ Keratinocyte activation→ ↑ TNFα & IL-6

- • Efficacy of IVIG treatment
- • SNS neurons as autoimmune targets
- • Antibodies against M-2 & β2-AR
- • ≠ CD8+ T-cell levels in blood

- ▪ Spinal microgliosis
- ▪ ↑ CSF glutamate
- ▪ ≠ cortical representation of affected limb
- ▪ ≠ in thalamus, S1, amygdala, perirhinal cortex, & hippocampus

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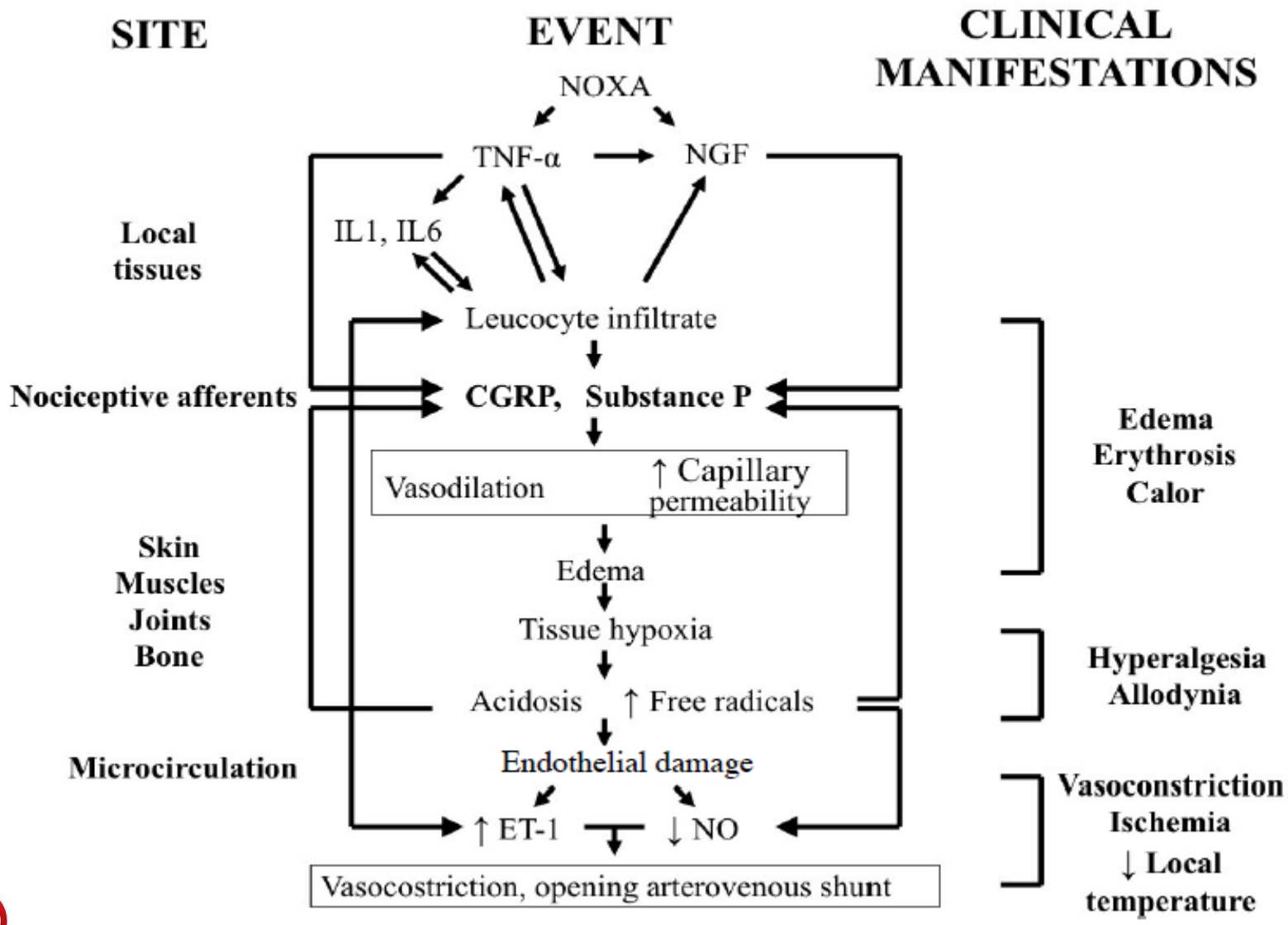
Tajerian et al. Hand Clin 2016

Possible pathogenic mechanisms in CRPS I and related clinical manifestations



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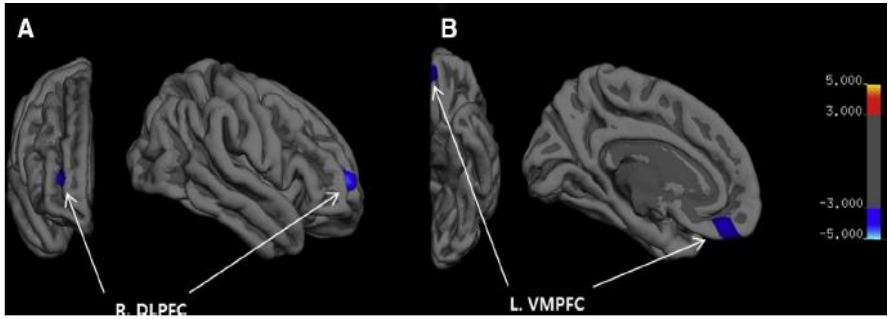
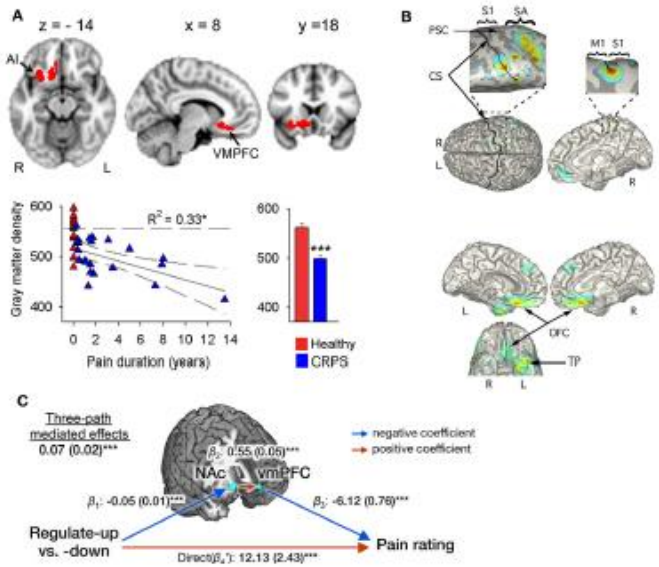
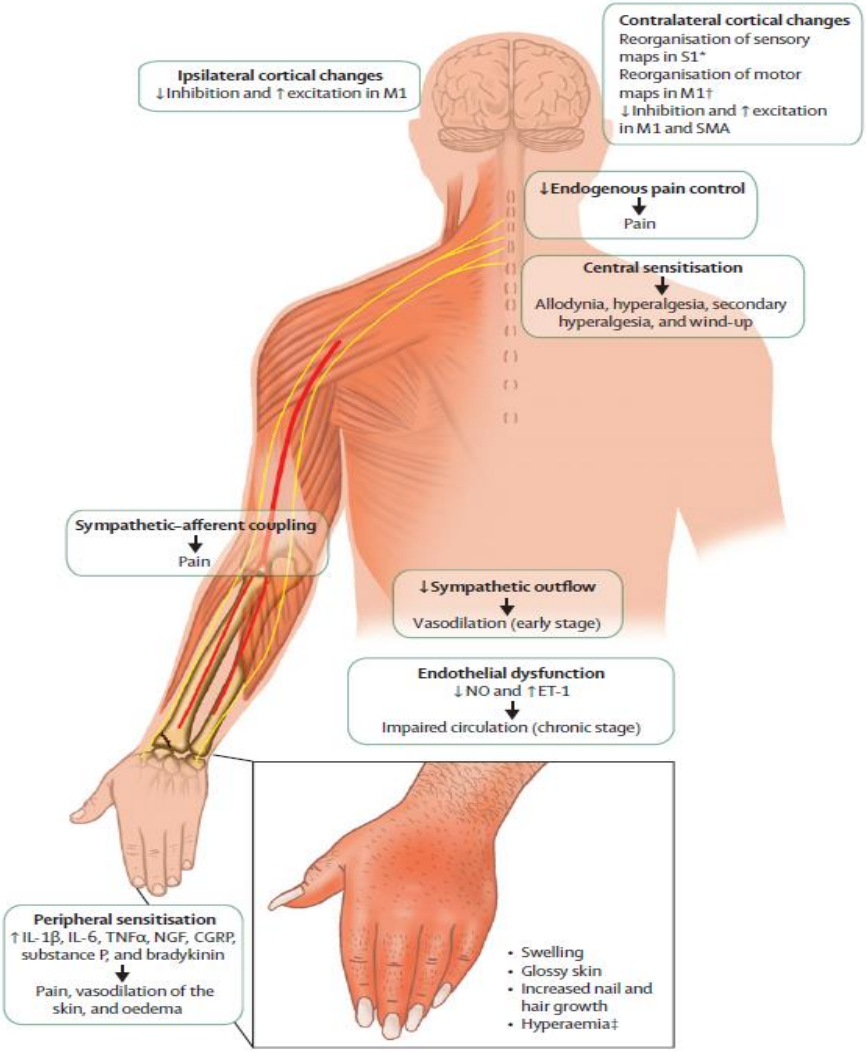
Varenna M. Yearbook, 2011

Clinical features and proposed pathophysiological mechanisms of CRPS







Marinus et al. Lancet Neurol 2011
Do-Hyeong et al J Pain 2015
Kuttikat et al. Front Hum Neurosc 2016

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Rational diagnostic approach to CRPS

1 → 2 ↔ 3

Suspect CRPS:

1) Symptoms develop in relation to a limb trauma (usually within ~ 4-6 weeks)
2) Symptoms cannot be explained by the trauma any more
3) Symptoms affect a) the distal extremity, b) go beyond the trauma territory and c) beyond nerve/nerve root innervation territories
4) Other diseases are vigorously excluded

Are the diagnostic criteria (adapted IASP Budapest criteria) for CRPS fulfilled?

Symptom categories:
1) Hyperalgesia, "hyperesthesia", allodynia
2) Asymmetry of skin temperature and skin color
3) Asymmetry of sweating, edema
4) Reduced ROM beyond trauma joint, dystonia, tremor, weakness, changes of hair and nail growth

Diagnosis CRPS can be made if all 3 points are fulfilled:
1) Continuing pain
2) Report of ≥ 1 symptom from 3 out of the 4 above symptom categories in history
3) Display of ≥ 1 symptom from 2 out of the 4 above symptom categories at time of investigation

Use additional diagnostic tools if clinical diagnosis is doubtful or testimony is expected

1) Longterm or repetitive skin temperature measurement: side to side difference >1-2°C
2) Three-phase bone scintigraphy (TPBS) using 99mTc-DPD: Ribbon-like tracer accumulation distant from trauma site
3) Side-by-side X-ray: Spotty decalcification
4) NMR: Bone marrow oedema

↓

Diagnosis "CRPS"

Differentiation

CRPS I: Without verified nerve lesion
CRPS II: With verified nerve lesion

Possible differentiation
"Primary warm": Skin temperature increased at the beginning ("inflammation type")
"Primary cold": Skin temperature decreased at the beginning (possibly poorer prognosis)

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modified from: Birklein et al. Neurology 2015

SIOMMMS guidelines

La mancanza di riferimento alla patologia dell'osso rende anche ragione della creazione dell'acronimo Chronic Regional Pain Syndrome (CRPS) secondo una dizione concentrata esclusivamente sul parametro clinico del dolore che si allontana dalla originaria e più complessiva descrizione del quadro clinico secondo Sudeck che al contrario aveva il merito di mantenere al centro dello scenario clinico la patologia dell'osso [3].

Il limite principale dei criteri di Budapest sta quindi nell'aver ignorato le alterazioni scheletriche quale evento fondamentale nella patogenesi della SA.

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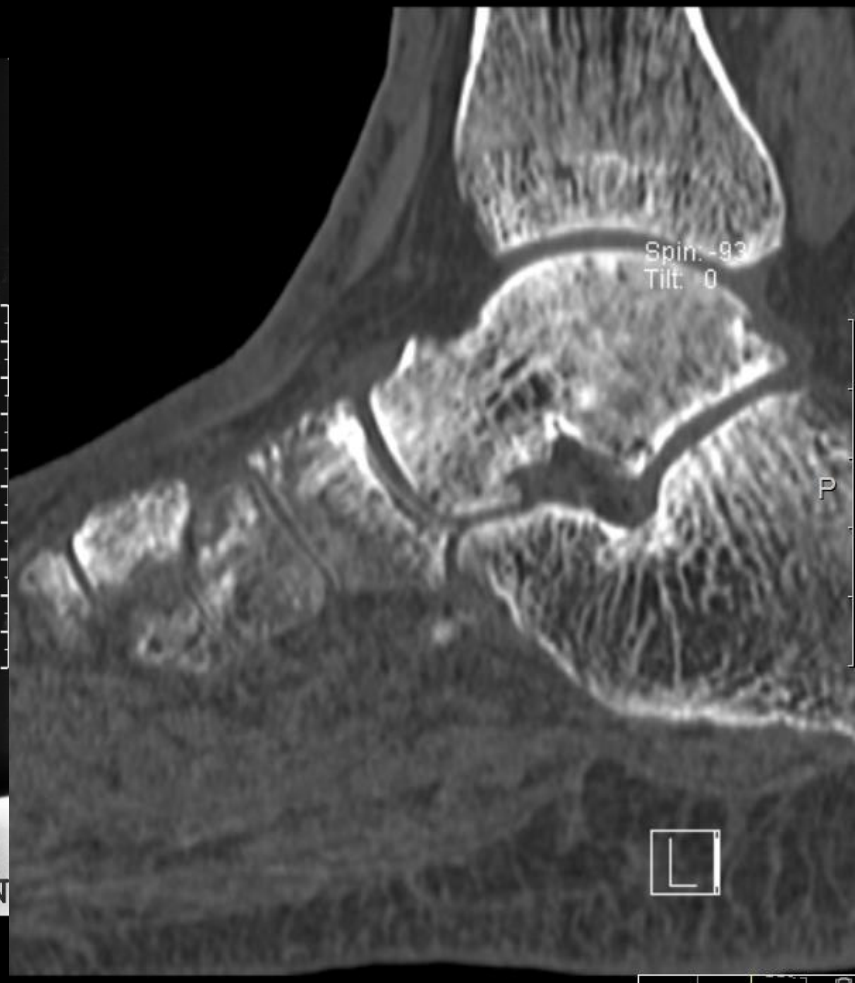

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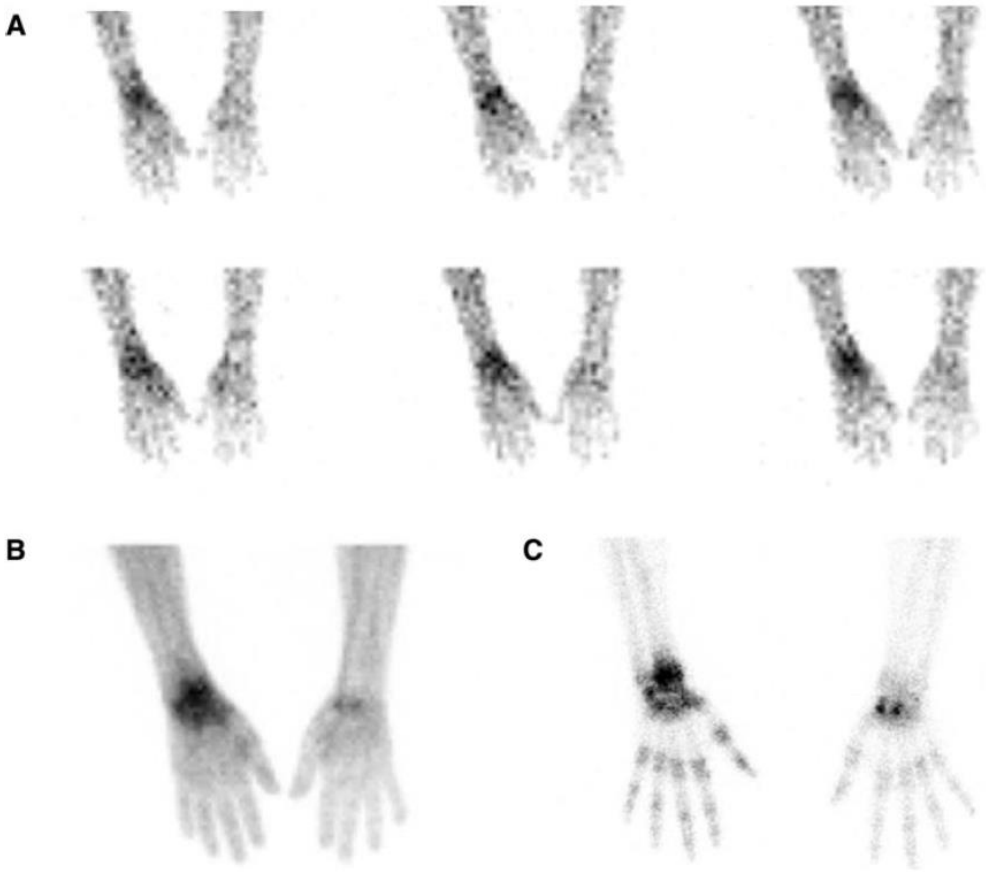
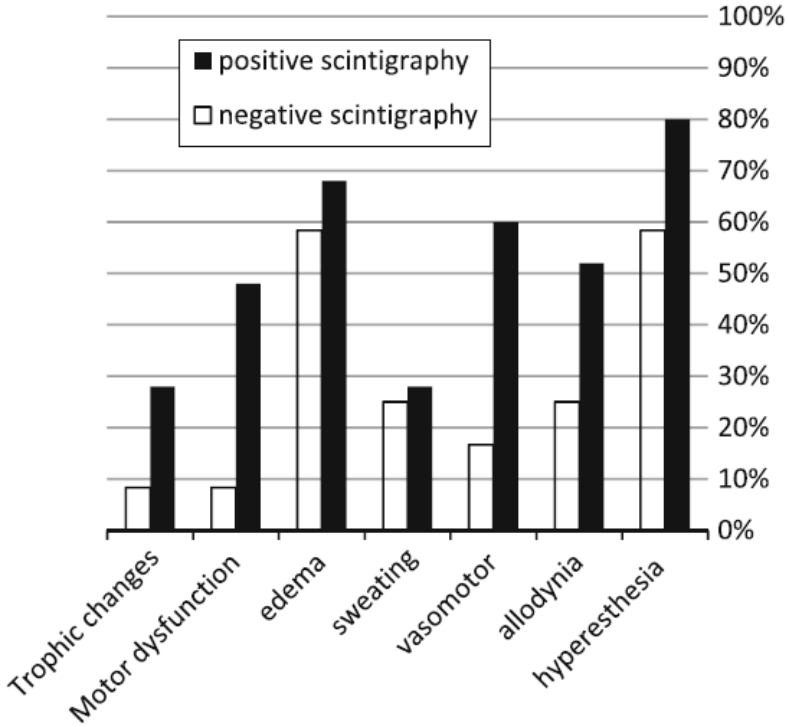
Bone scintigraphy





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AlSharif et al. Ann Nucl Med 2012

NMR

T1W sequences: Hypointense

T2W sequences: Hyperintense

FAT/SAT sequences: Hyperintense

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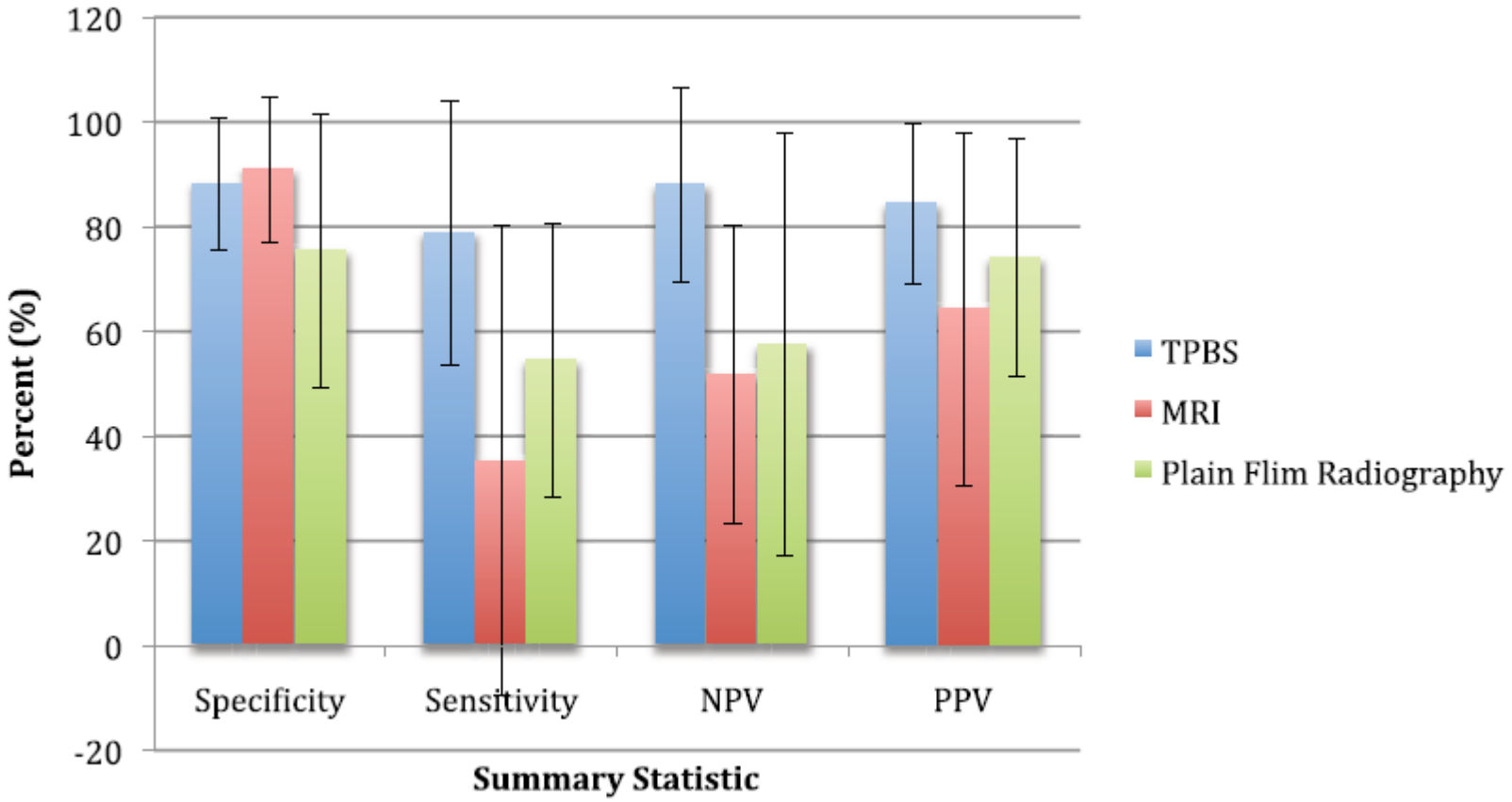
Meta-analysis of imaging techniques in CRPS-I



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Capello et al.J Hand Surg 2012

Bone Marrow Edema Etiology

- **Trauma**
  - Fracture (acute, osteoporotic, stress)
  - Local transient osteoporosis
  - Bone bruise
  - Osteochondral injuries
- **Degenerative lesions**
  - Osteoarthritis
- **Inflammatory lesions**
  - Inflammatory arthropaties and enthesitis
- **Vascular lesions**
  - Avascular necrosis
  - CRPS I
  - Sickle cell anemia
- **Infectious lesions**
  - Osteomyelitis
  - Diabetic foot, Charcot arthropaty
  - Sepsis
- **Metabolic/endocrine lesions**
  - Hydroxyapatite deposition disease (HADD)
  - Gout
- **Iatrogenic lesions**
  - Local surgery
  - Radiotherapy
- **Neoplastic (and neoplastic-like lesions)**

BONE VASCULAR SYNDROMES

- **Osteonecrosis**
- **Regional Osteoporosis**

1. CRPS-I
2. Bone Marrow Edema syndromes
   - Regional Migratory Osteoporosis (RMO)
   - Transient Osteoporosis of the Hip (TOH)

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modified from: Eriksen et al. Rheumatol Int, 2012

Summary of treatments for CRPS

Treatment	Category	Supporting RCT status
Multidisciplinary treatment	Standard	None
Physical and occupational therapy	Standard	Positive[150 153]
Oral corticosteroids (for acute CRPS)	Standard	Positive[150 162]
Anticonvulsants	Standard	Equivocal[164]
Analgesic antidepressants	Standard	None
Transdermal lidocaine	Standard	None
Opioids	Standard	None
Sympathetic nervous system blocks	Standard	Negative[150 153]
Spinal cord stimulation	Standard	Positive (<5 year efficacy)[167 168]
Pain focused psychological therapy	Standard	None
Graded motor imagery or mirror therapy	Uncommon	Positive[153 158]
Calcitonin	Uncommon	Positive[153]
Vitamin C (prevention after injury)	Uncommon	Positive[150 171-174 176]
Topical dimethylsulfoxide (DMSO)	Uncommon	Positive (warm CRPS)[150]
Oral N-acetylcysteine	Uncommon	Positive (cold CRPS)[150]
Bisphosphonates	Emerging	Positive[150 153 181-184]
Subanesthetic intravenous ketamine	Emerging	Positive[150 153 186 187]
Intravenous immunoglobulin	Emerging	Positive[189]
Oral tadalafil	Emerging	Positive[190]
Intrathecal baclofen (CRPS + dystonia)	Emerging	Positive[191]
Low dose oral naltrexone	Emerging	None

RCT=randomized controlled trial.

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Bruhel S . BMJ 2015

Cochrane Library

Cochrane Database of Systematic Reviews

Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II (Review)

Smart KM, Wand BM, O'Connell NE

AUTHORS' CONCLUSIONS

Implications for practice

It is likely that, in line with contemporary clinical guidelines, physiotherapy and rehabilitation based interventions will continue to be first-line treatments for people with complex regional pain syndrome (CRPS). In this Cochrane review we have been unable to find compelling evidence of the effectiveness, or lack thereof, of physiotherapy interventions, or to inform an optimal approach to therapy, although very low quality evidence suggests a possible benefit of multimodal physiotherapy, graded motor imagery (GMI) and mirror therapy. The available evidence suggests that applying ultrasound to the stellate ganglion or manual lymphatic drainage (MLD) to the affected limb are unlikely to offer clinical benefit to people with CRPS type I.

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Smart et al. Cochrane Database Syst Rev 2016

CRPS-I and medical treatment: drugs proposed and their evidence

Treatment	No. of patients treated and control group	Type of the study	Results	Reference
Glucocorticoids	10 vs 11	RCT vs placebo	No effects on pain and other outcome	[28]
	30 vs 30 (CRPS-I following stroke)	RCT vs piroxicam	Clinical improvement higher than competitor	[29]
	13 vs 23	RCT vs placebo	Clinical improvement	[30]
Immunoglobulin i.v.	6 vs 6	RCT vs placebo	Clinical improvement	[31]
Non-steroidal anti-inflammatory drugs	30 vs 30 (CRPS-I following stroke)	RCT vs glucocorticoid	Clinical improvement lower than competitor	[29]
Free radical scavengers	16 vs 16	RCT: Topical treatment with a cream with dimethyl sulfoxide (DMSO) vs topical treatment with a cream without DMSO	The clinical improvement in patients treated with DMSO was significantly better	[32]
	29 (no control group)	Retrospective study	Pain improvement	[33]
	73 vs 73	RCT: Topical dimethylsulfoxide (DMSO) vs oral acetylcysteine	Two treatments have similar clinical effects	[34]
Ketamine	30 vs 30 (Chronic CRPS-1)	RCT: vs placebo	Transitory pain improvement: the higher effect was seen after 1 week, but in week 12, significance in pain relief between groups was lost	[35]
	9 vs 10	RCT: vs placebo	Pain improvement	[36]

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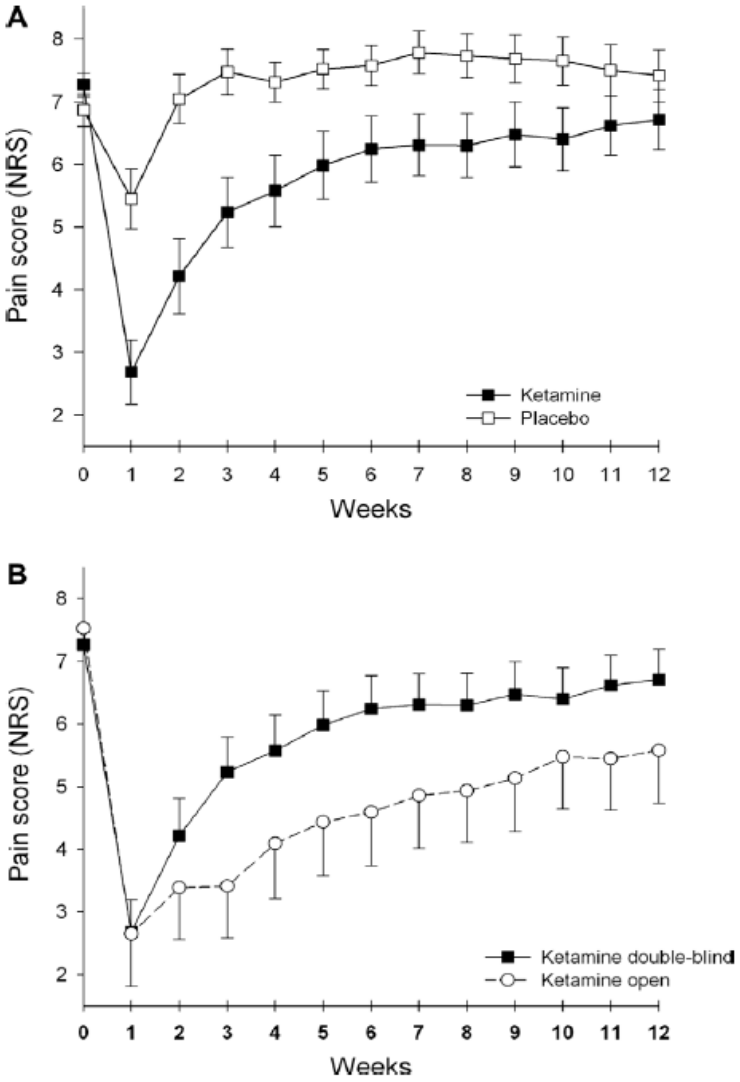
Gatti et al. Osteoporos Int 2016

Ketamine in CRPS-I

Sixty CRPS-1 patients (48 females) with severe pain participated in a double-blind randomized placebo-controlled parallel-group trial. Patients were given a 4.2-day intravenous infusion of low-dose ketamine ($n = 30$) or placebo ($n = 30$) using an individualized stepwise tailoring of dosage based on effect (pain relief) and side effects (nausea/vomiting/psychomimetic effects). The primary outcome of the study was the pain score (numerical rating score: 0–10) during the 12-week study period. The median (range) disease duration of the patients was 7.4 (0.1–31.9) years. At the end of infusion, the ketamine dose was 22.2 ± 2.0 mg/h/70 kg. Pain scores over the 12-week study period in patients receiving ketamine were significantly lower than those in patients receiving placebo ($P < 0.001$). The lowest pain score was at the end of week 1: ketamine 2.68 ± 0.51, placebo 5.45 ± 0.48. In week 12, significance in pain relief between groups was lost ($P = 0.07$). Treatment did not cause functional improvement. Patients receiving ketamine more often experienced mild to moderate psychomimetic side effects during drug infusion (76% *versus* 18%, $P < 0.001$). In conclusion, in a population of mostly chronic CRPS-1 patients with severe pain at baseline, a multiple day ketamine infusion resulted in significant pain relief without functional improvement. Treatment with ketamine was safe with psychomimetic side effects that were acceptable to most patients.



Sigtermans et al. Pain 2009

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Local anaesthetic sympathetic blockade for CRPS

Comparison 1. Local anaesthetic block versus normal saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients who achieved at least 50% of pain relief	2	46	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.84]

Analysis 1.1. Comparison 1 Local anaesthetic block versus normal saline, Outcome 1 Number of patients who achieved at least 50% of pain relief.

Review: Local anaesthetic sympathetic blockade for complex regional pain syndrome

Comparison: 1 Local anaesthetic block versus normal saline

Outcome: 1 Number of patients who achieved at least 50% of pain relief

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Price 1998	6/7	6/7		58.5 %	1.00 [0.65, 1.53]
Verdugo 1995	12/16	8/16		41.5 %	1.50 [0.85, 2.64]
Total (95% CI)	**23**	**23**		**100.0 %**	**1.18 [0.76, 1.84]**

Total events: 18 (Treatment), 14 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.61$, df = 1 (P = 0.20); $I^2 = 38\%$

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

This update reveals little progress in developing high quality evidence to support this intervention since the last updates in 2005 and 2010. There are only three placebo-controlled randomised studies that met our inclusion criteria (Aydemir 2006; Price 1998; Verdugo 1995), all of which have very small sample sizes. No firm conclusions can be drawn from this evidence. It is notable that the results to date are not suggestive of a significant effect of LASB over placebo even in the very short term (30 minutes to two hours). We could not estimate the duration of pain relief, if any.

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Stanton et al. Cochrane Database Syst Rev 2013

1. L'edema osseo riscontrabile con la RMN, associato alla ipercaptazione scintigrafica del tracciante documenta una condizione infiammatoria locale che si traduce in un alterato turnover scheletrico regionale.
2. Studi epidemiologici dimostrano che l'osteoporosi è la patologia più frequentemente associata alla SA [4].
3. Il modello animale di frattura della tibia del ratto è quello che più fedelmente riproduce la SA umana [5].
4. La perdita di densità ossea regionale si verifica in tempi brevi e non può quindi essere spiegata come secondaria alla sofferenza neurologica [6].
5. La riduzione della sintomatologia clinica che fa seguito alla terapia con bisfosfonati è molto spesso definitiva per cui è possibile sostenere che la terapia con dosi adeguate di bisfosfonati "cura" la malattia, mentre è ragionevole escludere che possa risolvere anche momentaneamente un aspetto finora ritenuto patogeneticamente irrilevante della malattia.
6. I più frequenti eventi predisponenti coinvolgono sistematicamente il tessuto scheletrico [7].

Bisphosphonates in CRPS-I

Table 1 Randomised controlled trials investigating the effects of bisphosphonates in complex regional pain syndrome type I: characteristics of the trials

References	Jadad Score	Treatment: Active	Treatment: Control	Number of patients (F)	Age (years) Mean (SD) or Range	Diagnostic criteria	Disease duration (weeks or months) Mean (SD)	Follow-up (days) Double-blind (Open-label)	Additional treatment
Adami S *et al*[31]	3	Alendronate 7.5 mg intravenous for 3 days	Placebo intravenous for 3 days	20 (12)	39–80	Kozin	ALD: 16 (17) weeks PLB: 19 (19) weeks	14 (+14)	Physical therapy
Varenna M *et al*[21]	5	Clodronate 300 mg intravenous for 10 days	Placebo intravenous for 10 days	32 (19)	56 (9)	Kozin	4.0 (2.3) months	40 (+140)	None
Robinson JN *et al*[32]	3	Pamidronate 60 mg intravenous single time	Placebo intravenous single time	27 (9)	30–60	IASP	21.6 (NR) months	90	Paracetamol, codeine, dextropropoxyphene
Manicourt DH *et al*[33]	5	Alendronate 40 mg oral for 56 days	Placebo oral for 56 days	39 (21)	45 (12)	IASP Budapest	ALD: 7 (2) months PLB: 8 (3) months	84 (+84)	Physical therapy
Varenna M *et al*[34]	5	Neridronate 100 mg intravenous four times	Placebo intravenous four times	82 (53)	NRD: 58 (13) PLB: 57 (10)	Budapest	NRD: 4.7 (4.1) weeks PLB: 5.0 (4.6) weeks	40 (+50)	NSAIDs, paracetamol

ALD, alendronate; CRPS, complex regional pain syndrome; Double-blind, during the double-blind phase of the study; F, female; iv, intravenous; IASP, International Association for the Study of Pain; NR, not reported; NRD, neridronate; Open-label, during the open-label phase of the study; NSAIDs, non-steroidal anti-inflammatory drugs; PLB, placebo.

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Giusti et al. RMD Open 2015

Bisphosphonates in CRPS-I

Study	No. of patients	Age, years	M/F	Disease duration	Post-traumatic, %	Intervention	Main results	Study duration	Follow-up, months
Adami *et al.*, Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997; 56: 201–4	20	Range 39–80	8/12	Range 5–34 weeks	80	Alendronate 7.5 mg i.v. daily for 3 days	VAS: −62% Tenderness improved Motion score improved	4 weeks	12
Varenna *et al.*, Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind placebo controlled study. J Rheumatol 2000; 27: 1477-83	32	55.6 (8.6)	13/19	4.0 (2.3) months	66	Clodronate 300 mg i.v. daily for 10 days	VAS: −62% Global clinical assessment improved Patient's perceived efficacy improved	40 days	12
Robinson *et al.*, Efficacy of pamidronate in complex regional pain syndrome type I. Pain Med 2004; 5: 276–80	37	Mean [illegible] (range 30–60)	9/18	Mean 21 [illegible] (range 5–72) months	NR	Pamidronate 60 mg i.v. in a single dose	VAS improved P = 0.04 SF-36 improved Patient's global assessment improved	3 months	NR
Manicourt *et al.*, Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. Arthritis Rheum 2004; 50: 3690–7	40	Treated, 44.6 (12.3); placebo, 45.2 (12.5)	19/21	Treated, 7 (2) months; placebo, 8 (3) months	100	Alendronate 40 mg p.o. daily for 8 weeks	VAS: −67% Pressure tolerance improved Oedema decreased Joint mobility improved	8 weeks	NR
Varenna *et al.*, Treatment of complex regional pain syndrome with neridronate: a randomized double-blind placebo-controlled study. Rheumatology 2013; 52: 534–42	82	Treated, 58.2 (12.7); placebo, 57.0 (10.3)	29/53	Treated, 4.7 (4.1) weeks; placebo, 5.0 (4.6)	65	Neridronate 100 mg i.v. every third day four times	VAS: −66% McGill pain questionnaire improved SF-36 improved Oedema decreased Passive motion increased Allodynia improved Hyperalgesia improved	40 days	14

None of these 4 trials provided sufficient data to validate the use of bisphophonates in CRPS-I

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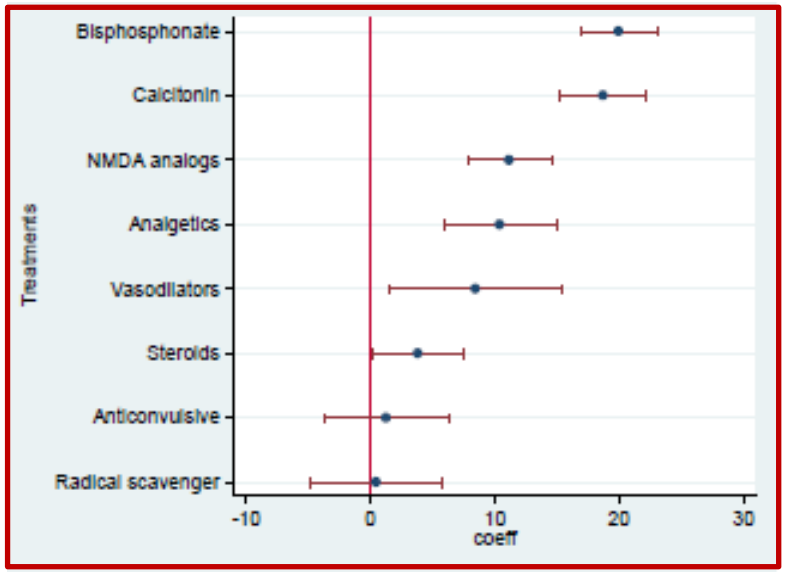
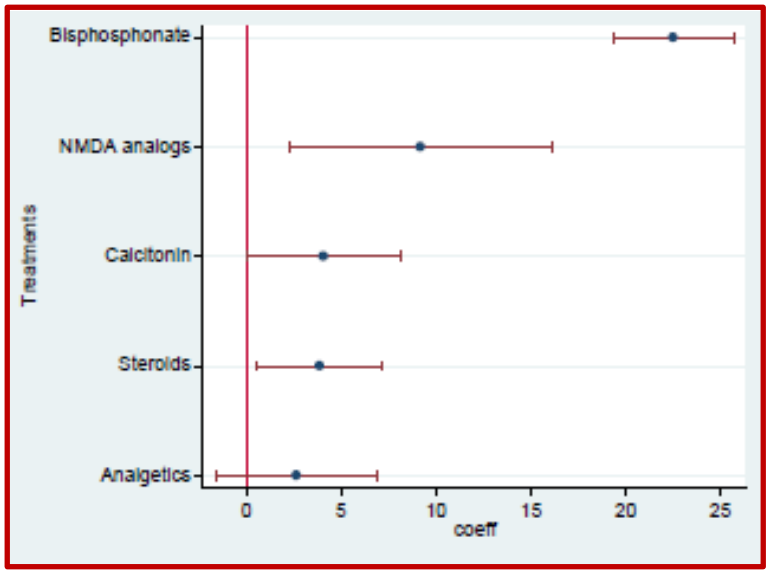
Varenna M. Rheumatology 2014

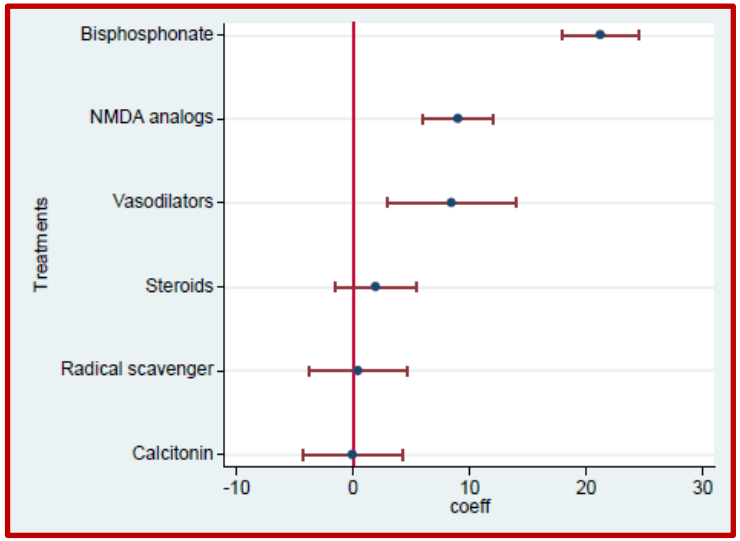
Pain management in CRPS-I: meta-analysis

Overall treatment efficacy



Result in mean symptoms duration less than 12 mo





Results of follow-up 2 months and more

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Wertli et al. Pain Med 2014

RHEUMATOLOGY

Rheumatology 2013;52:534–542
doi:10.1093/rheumatology/kes312
Advance Access publication 30 November 2012

Original article

Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study

Massimo Varenna[1], Silvano Adami[2], Maurizio Rossini[2], Davide Gatti[2], Luca Idolazzi[2], Francesca Zucchi[1], Nazzarena Malavolta[3] and Luigi Sinigaglia[1]

Objective. Complex regional pain syndrome type I (CRPS-I) is a severely disabling pain syndrome for which no definite treatment has been established. The aim of this multi-centre, randomized, double-blind placebo-controlled trial was to test the efficacy of the amino-bisphosphonate neridronate in patients with CRP-I.

Methods. Eighty-two patients with CRP-I at either hand or foot were randomly assigned to i.v. infusion of 100 mg neridronate given four times over 10 days or placebo. After 50 days the former placebo patients were given open label the same regimen of neridronate.

Results. Within the first 20 days, visual analogue scale (VAS) score decreased significantly more in the neridronate group. In the following 20 days, VAS remained unchanged in the placebo group and further decreased in the active group by 46.5 mm (95% CI −52.5, −40.5) *vs* 22.6 mm (95% CI −28.8, −16.3) for placebo group ($P < 0.0001$). Significant improvements *vs* placebo were observed also for a number of other indices of pain and quality of life. During the open-extension phase in the formerly placebo group the results of treatment were superimposable on those seen during the blind phase in the active group. A year later none of the patients was referring symptoms linked to CRPS-I.

Conclusion. In patients with acute CRPS-I, four i.v. infusions of neridronate 100 mg are associated with clinically relevant and persistent benefits. These results provide conclusive evidence that the use of bisphosphonates, at appropriate doses, is the treatment of choice for CRPS-I.

Trial registration: EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/, 2007-003372-18.

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RHEUMATOLOGY

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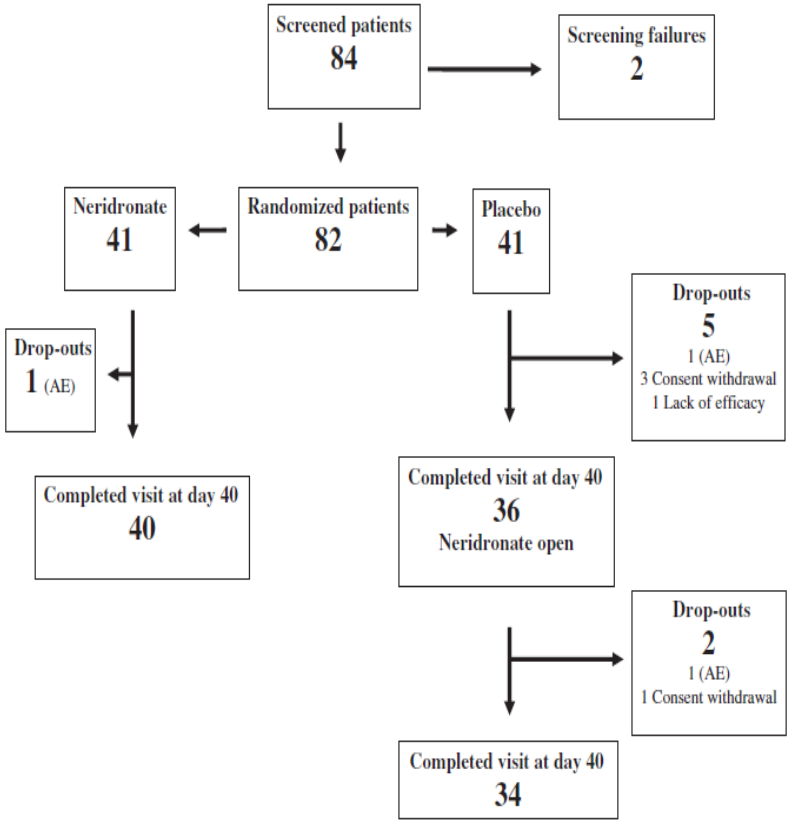

	Neridronate ($n = 41$)	Placebo ($n = 41$)	P
Age, mean (S.D.), years	58.2 (12.7)	57.0 (10.3)	0.6
Gender, M/F, n	16/25	13/28	0.6
Disease duration, mean (S.D.), weeks	4.7 (4.1)	5.0 (4.6)	0.7
Precipitating event, n (%)			
Fracture	11 (26.8)	17 (41.4)	0.2
Trauma	10 (24.4)	7 (17.1)	0.5
Surgery	5 (12.2)	4 (9.8)	0.9
Unknown	15 (36.6)	13 (31.7)	0.8
Site, n (%)			
Upper limb	8 (19.5)	12 (29.3)	0.4
Lower limb	33 (80.5)	29 (70.7)	

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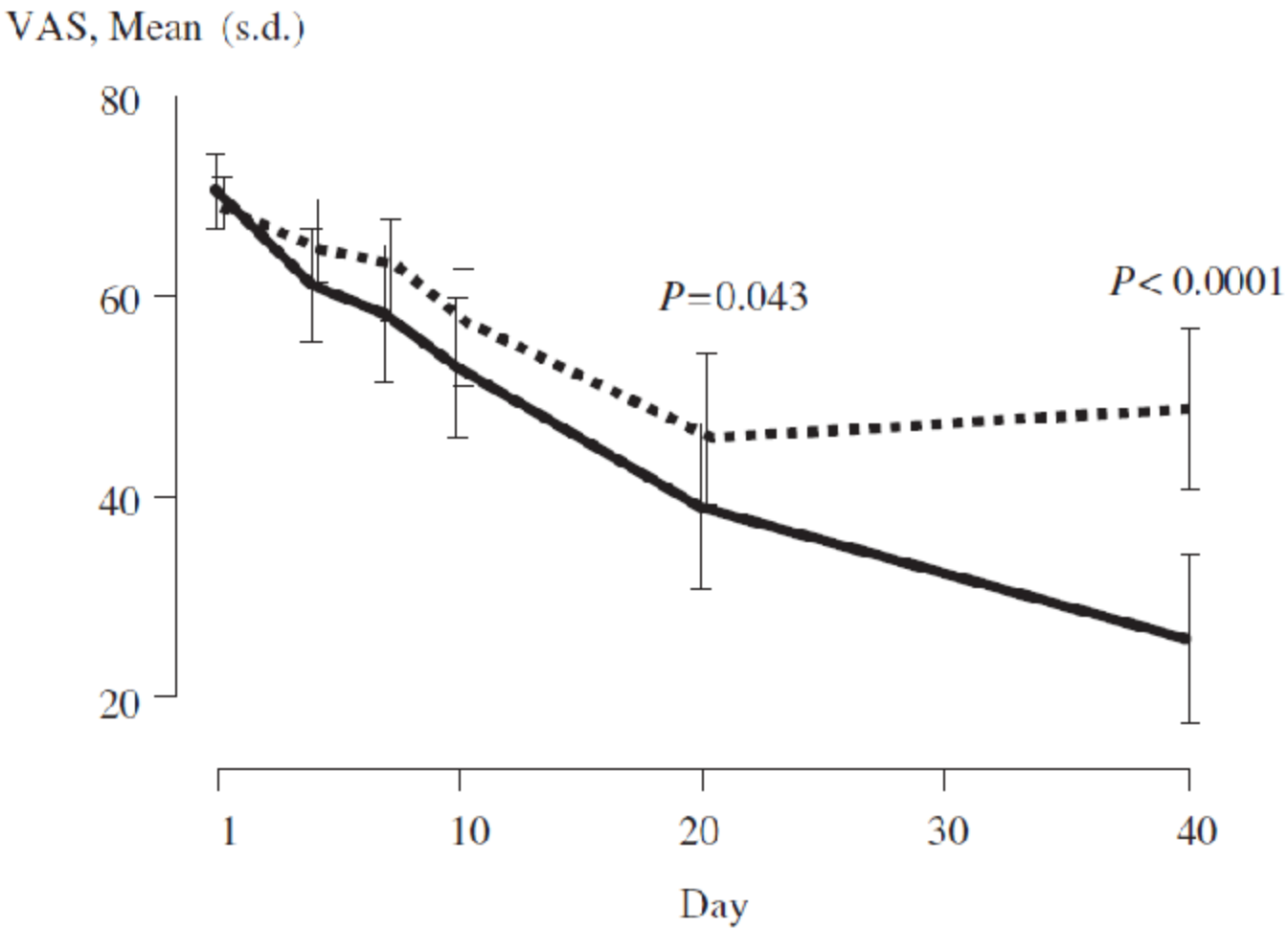

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RHEUMATOLOGY

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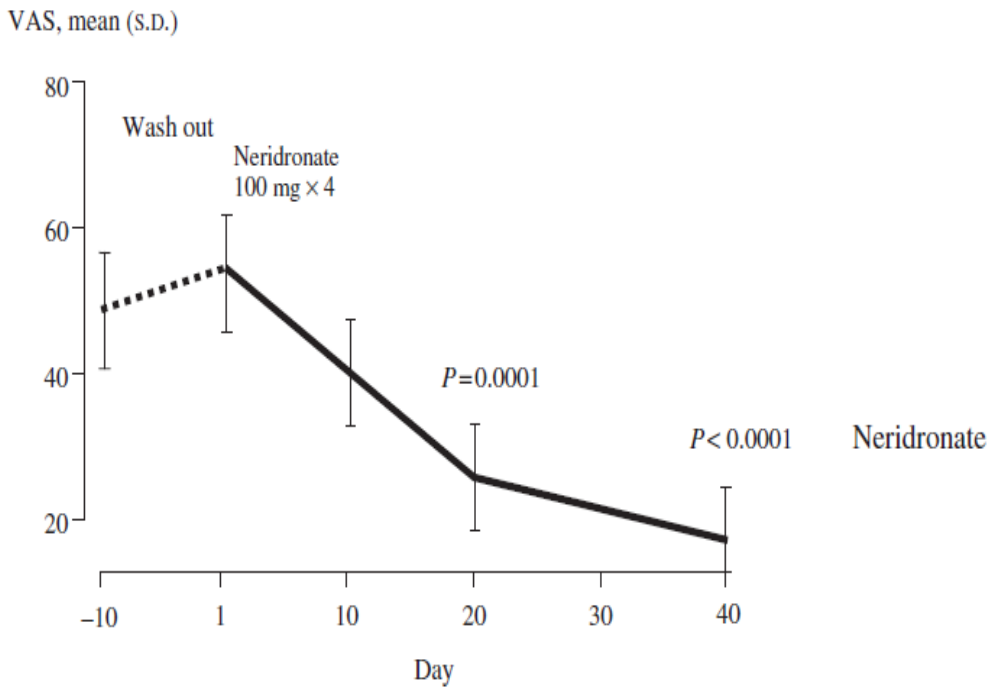
FIG. 3 VAS values at the end of the follow-up period of the double-blind phase (day −10) and after the treatment course with i.v. neridronate in patients with CRPS-I.



A year later, none of the patients was referring symptoms linked to CRPS-1.
Bone scintigraphy control was obtained in 36 pts with complete normalization.
In 12 pts MRI negative for bone marrow edema.
No serious drug-related AEs

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Table 3 Changes in VAS and proportion of responders during the open-label extension phase of the study in patients with CRPS-I treated with neridronate

Assessments	Start of open phase ($n = 36$)	Day 40 ($n = 34$)	P value
Pain assessment			
Pain assessed on VAS (mm), mean (S.D.)	55.4 (24.2)	13.9 (15.8)	<0.0001
Responders (pain decrease > 50%), n (%)	12 (33.3)[a]	28 (82.3)[b]	0.0015
Other clinical signs and symptoms			
Oedema (present[c]), n (%)	29 (80.6)	2 (5.9)	<0.0001
Pain at motion (present[c]), n (%)	34 (94.4)	14 (41.2)	<0.0001
Allodynia (present), n (%)	19 (52.8)	0 (0.0)	<0.0001
Hyperalgesia (present), n (%)	22 (61.1)	0 (0.0)	<0.0001
SF-36			
Physical functioning, mean (S.D.)	52.6 (29.7)	71.5 (19.3)	<0.0001
Role limitations due to physical health, mean (S.D.)	38.2 (44.9)	58.8 (43.5)	0.0073
Role limitations due to emotional problems, mean (S.D.)	51.9 (44.7)	68.6 (39.3)	0.043
Energy/fatigue (vitality), mean (S.D.)	50.1 (22.5)	58.7 (14.5)	0.024
Emotional well-being (mental health), mean (S.D.)	54.9 (20.6)	63.6 (16.2)	0.011
Social functioning, mean (S.D.)	52.8 (26.6)	69.5 (20.9)	0.0001
Pain, mean (S.D.)	36.9 (15.8)	61.4 (21.8)	<0.0001
General health, mean (S.D.)	45.4 (18.4)	54.1 (17.0)	0.006
Physical component scale, mean (S.D.)	35.5 (9.0)	43.3 (9.0)	<0.0001
Mental component scale, mean (S.D.)	42.5 (11.1)	46.2 (9.0)	0.121
McGill Pain Questionnaire			
Sensory items, mean (S.D.)	11.5 (6.7)	3.8 (4.1)	<0.0001
Affective items, mean (S.D.)	3.8 (3.4)	1.0 (1.3)	<0.0001

[a]In comparison with baseline values. [b]In comparison with start of the open phase. [c]Of any degree (mild, moderate or severe).

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Pamidronate vs prednisolone in CRPS-I

Prednisolone 1 mg/kg tapered over 2 weeks
Pamidronate 60 mg e.v. every other day for 3 infusions

Methods: Twenty-one hemiplegic stroke patients with CRPS type I were enrolled in the study. Patients were randomly assigned to receive either intravenous pamidronate (n = 11; total cumulative dose of 180 mg) or oral prednisolone (n = 10). Subjective pain and hand oedema (circumference of the middle finger, CMF, and the wrist, CW) were measured at baseline and at one, two and four weeks after the end of treatment.

Table 1. *General patient characteristics*

	Steroid (n = 10)	Pamidronate (n = 11)	*p* value
Age (years)	67.50±6.95	63.09±10.53	0.31
Gender (male:female)	5:5	5:6	1.00
Type of stroke (ischaemia: haemorrhage)	4:6	6:5	0.67
Side of affected hand (right:left)	5:5	3:8	0.39
MMSE score	26.00±1.70	26.0±1.41	0.91
Onset duration since stroke occurrence (days)	47.90±18.25	54.91±33.02	0.55
VAS	6.10±0.88	6.55±1.13	0.22
CMF-affected	7.34±0.34	7.51±0.48	0.22
CMF-unaffected	6.66±0.44	6.89±0.47	0.22
CW-affected	17.46±0.95	17.59±0.96	0.47
CW-unaffected	16.36±0.65	16.68±1.09	0.17

VAS = visual analogue scale; MMSE = mini-mental status examination; CMF = circumference of the middle finger; CW = circumference of the wrist. Values are presented as mean± standard deviation (SD).

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Pamidronate vs prednisolone in CRPS-I

Results: Both groups showed significant improvement in subjective pain VAS scores at 1-week follow-up and this effect was maintained until 4-week follow-up. Time-by-group interactions were not significant at 4-week follow-up. The reduction of the CMF observed at 1-week follow-up in both groups was maintained until 4-week follow-up in the steroid group, but until 2-week follow-up in the pamidronate group. A significant change in CW was observed at 4-week follow-up in the pamidronate group. There were no significant adverse effects in either treatment group during the follow-up period.

Conclusions: Intravenous pamidronate therapy was safe, well tolerated and appeared as effective as a steroid for pain control for post-stroke CRPS. However, this result should be interpreted with caution, since it included a relatively small number of patients. Further larger controlled studies followed over a longer period are needed to validate these findings and to determine clinical treatment standards.

Table 2. *Visual analogue scale change after the end of steroid and pamidronate therapy*

	VAS		
	Steroid	Pamidronate	Time-by-group Interactions (*p* value)
Baseline	6.10±0.88	6.55±1.13	
1 week	5.20±0.79†	4.64±1.29‡	0.014*
2 week	4.90±1.10‡	4.27±1.15‡	0.041*
4 week	4.60±0.84‡	4.00±1.90‡	0.205

VAS = visual analogue scale. Values are mean ± SD. Statistical significance compared with baseline at †$p < 0.05$ level, and ‡$p < 0.01$ (intra-group differences). Statistical significant time-by group interactions at *$p < 0.05$ level, and **$p < 0.01$ (inter-group differences).

Table 3. *Change in circumference of the middle finger after the end of steroid and pamidronate therapy*

	CMF: Affected side (cm)		
	Steroid	Pamidronate	Time-by-group interactions
Baseline	7.34±0.34	7.51±0.48	
1 week	7.09±0.36‡	7.31±0.42†	0.585
2 week	6.94±0.28‡	7.30±0.41†	0.092
4 week	6.94±0.33†	7.31±0.51	0.122

CMF = circumference of the middle finger. Values are mean ± SD. Statistical significance compared with baseline at †$p<0.05$ level, and ‡$p<0.01$ (intra-group differences).

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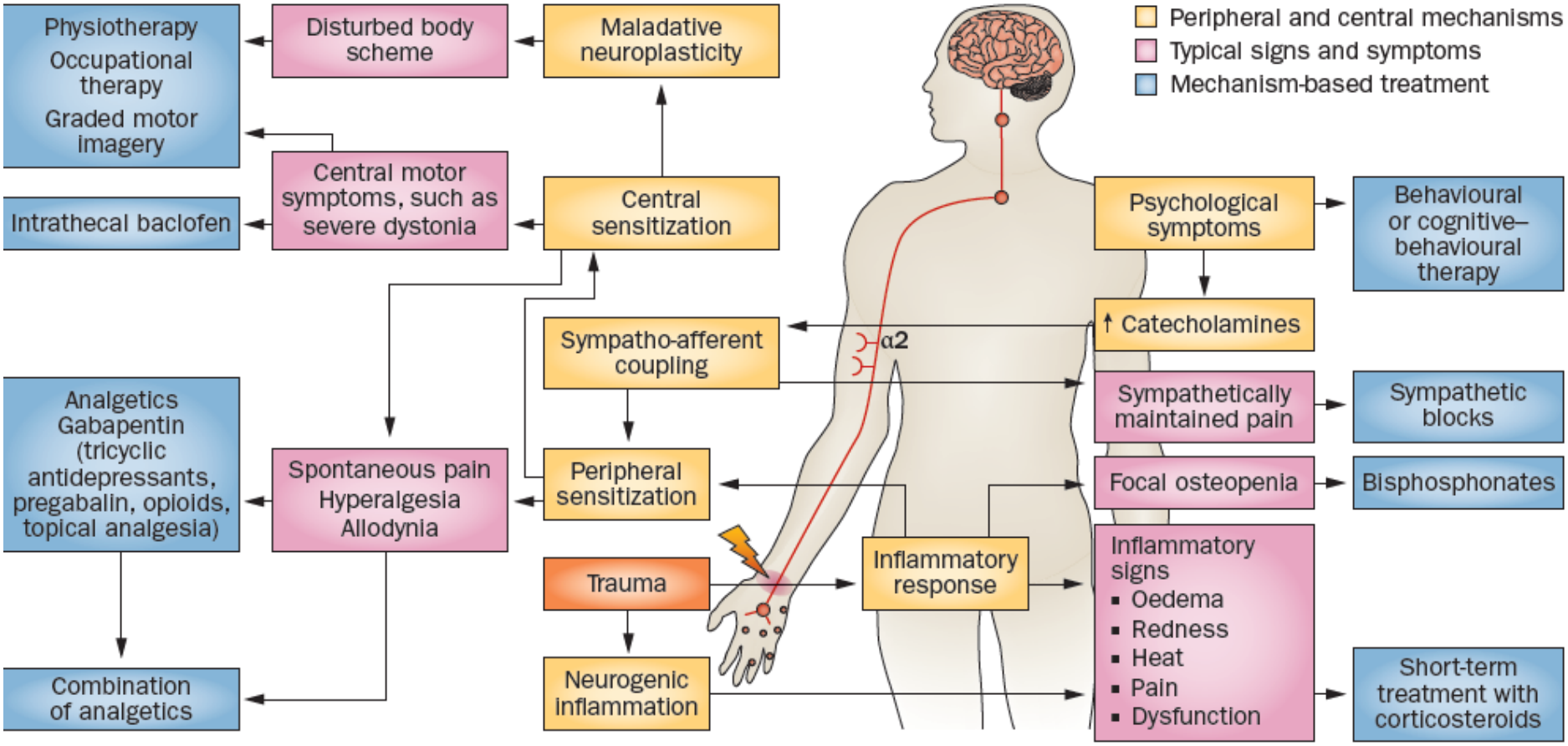
Eun Young et al. Neth J Med 2016

Pathophysiology and mechanism-based treatment options in CRPS



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Giertmühlen et al. al. Nat. Rev. Neurol 2014

How bisphosphonates could act in CRPS-I?

Canonical suppression of bone turnover?

Bone scan over uptake ed MRI “bone edema” could suggest an high turnover in bone area, but regional osteoporosis occurs too early to be explained by an osteoclast-mediated mechanism.
Furthermore the few studies available on bone turnover markers and on histopathological tissues did not show an increased osteoclastic activity even in the fist phases of CRPS-I, when bisphosphonates show their best effectiveness.

RHEUMATOLOGY

Rheumatology 2014;53:965-967
doi:10.1093/rheumatology/ket370
Advance Access publication 22 November 2013

Editorial

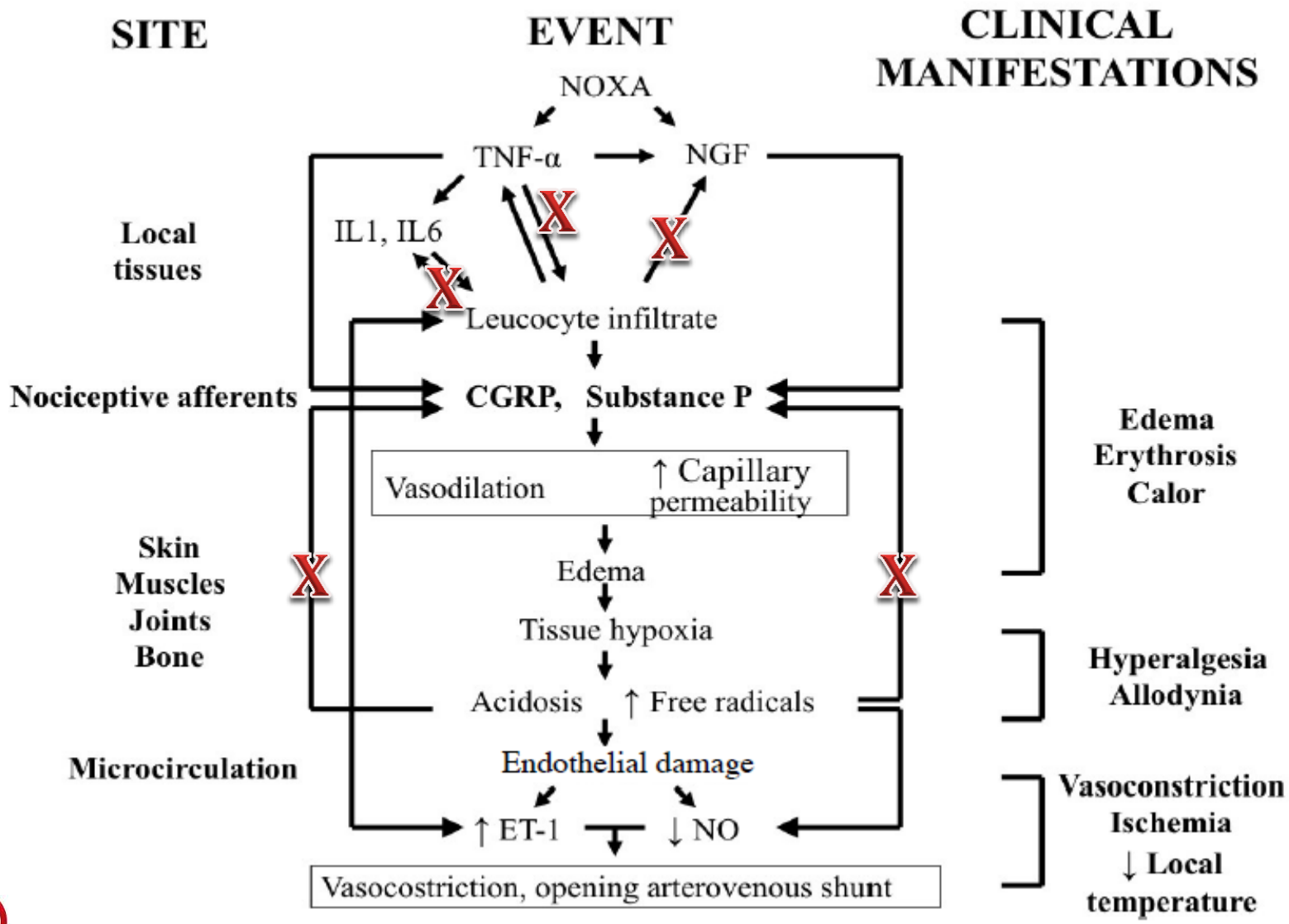
Bisphosphonates beyond their anti-osteoclastic properties

The lesson of complex regional pain syndrome

I.R.C.C.S. ISTITUTO ORTOPEDICO GALEAZZI

Varenna M. Rheumatology 2014

How bisphosphonates could act in CRPS-I?



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Modified from Varenna M. Yearbook, 2011

How bisphosphonates could act in CRPS-I?

Prevention of hydroxyapatite crystal dissolution in an acid milieu?

In high concentration bisphosphonates show this action

Reduction of lactic acid production?

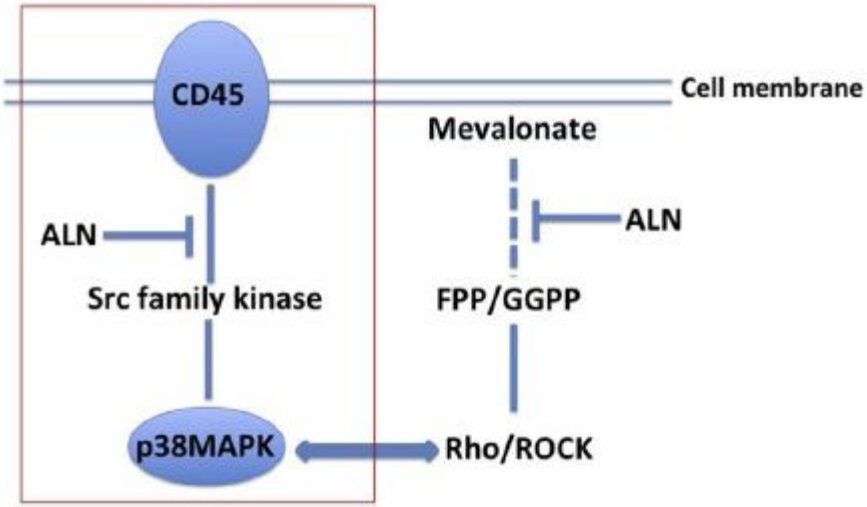
Bisphosphonates are able to reduce lactic acid production from different cells. Tissues acidosis and increased lactic acid in CRPS-I patients have been demonstrated to cause an antidromic release of CGRP (calcitonin-gene-related peptide) and substance P from nociceptive afferents.

How bisphosphonates could act in CRPS-I?

Inhibition of monocytes/macrophages?

Reduced production of pro-inflammatory cytokines and nerve growth factor (NGF), that promotes further differentiation and activation of monocyte/macrophage and other cells lineages, increases the expression of some acid-sensing receptors in sensory neurons and induces proliferation and activation of keratinocytes, probably involved in maintaining inflammation, nociceptive sensitization and microvascular disturbancies in CRPS-I.

How bisphosphonates could act in CRPS-I?



Microglia are regarded as the immune cells of the CNS and are quickly activated in response to external stimuli, releasing inflammatori cytokines (TNFα, IL-1β, IL-6) which play a critical role in the development and maintenance of central sensitization and hyperalgesia by altering the sensitivity of the afferent neurons, thus modulating the transmission of painful stimuli to the central nervous system

In chronic constriction injury animal models ALN administred intrathecally and intraperitoneally reduced in vivo (and in vitro cultures) the microglial activation and phosphorilation of p38 but did not reduce the expression of CD45. The result indicated that ALN might target some sites downstream of CD45, such as the Src/p38 MAPK signaling cascade, in spinal microglia

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Yao et al. J Pain 2016

Conclusions

- The pathophysiologic mechanisms of CRPS-I remain poorly understood

- Diagnostic criteria are focused on signs and symptoms (mainly of the cold and late phase) and do not include imaging findings (particularly bone scan and MRI) of the early stage of the disease

- Cold CRPS-I with worse prognosis and atrophic, often dramatic evolution is the late phase of a initially warm CRPS-I or are two distinct diseases?

- The efficacy of BPs in CRPS –I treatment raise new questions about the mechanism of CRPS-I and about the pleiotropic qualities of these drugs

- In cold-atrophic CRPS-I the effect of BPs and of other drugs seems low. It is of great importance to diagnose and treat the disease early.